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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/027,075	12/20/2001	Gary S. Gray	RPN-001CN	1776

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	5

DATE MAILED: 09/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/027,075	GRAY ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-59,61-63,65-67,69 and 92-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-59,61-63,65-67,69 and 92-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1.5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 56-59, 61-63, 65-67, 69, 92-94 are pending and under examination.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specifically the citizenship of Kashi Javaherian has been written in.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 56-59, 62, 65-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a CTLA4 fusion protein comprising residues 1-125 of CTLA4 and fusion to either IgG Cgamma4 constant regions, IgG Cgamma4 constant regions which have been modified by substitution of Leu at position 235 with Glu and Gly at position 237 with Ala, or fusion to IgG Cgamma4 constant regions which have been specifically modified by substitution of Leu at position 234 with Ala, Leu at position 235 with Glu and Gly at position 237 with Ala, does not reasonably provide enablement for a modified CTLA4-immunoglobulin fusion protein with just any

substitution, addition, or deletion of at least one residue in the immunoglobulin constant region other than those indicated above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to fusion proteins with any substitutions, deletions, or additions at any location in the constant region. Each of the rejected claims encompasses fusion proteins with unspecified modifications at any position and any number of multiple changes within the entire length of the protein. The specification does not provide adequate guidance and objective evidence regarding the predictability of the binding characteristics of the full scope of the encompassed fusion proteins. Guidance is provided regarding specific locations where modifications within the immunoglobulin constant regions predictably reduce Fc or complement binding. Screening of fusion proteins involving modifications at these positions would not require undue experimentation because the predictability of success is reasonably high. The screening assays provided may be routinely used to screen these candidate fusion

proteins having modifications at the specified locations without undue experimentation, in accord with the teachings of *In re Wands*.

The scope of the encompassed invention is not limited to fusion proteins having modifications in locations where reduced Fc and complement binding is predictable. The scope of the claimed invention encompasses modifications at any location and there is insufficient guidance and objective evidence to render it predictable that any modification at any location would reasonably result in the desired characteristics.

The amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be substituted within a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138, IDS 1 ½). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252, IDS 1 ½).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987, IDS 1 ½). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975, IDS 1 ½).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. Elucidation off the genetic code induces one to believe that one can readily obtain a functional synthetic protein for any known nucleic acid sequence with predictable results. The results of the modifications of proteins remain very unpredictable as Burgess et al, Lazar et al, Schwartz et al, Lin et al conclusively demonstrate.

Since detailed information regarding the structural and functional requirements of this protein are lacking, it is unpredictable as to which amino acid substitutions, if any, meet the limitations of the claim. While screening assays are provided and addressed in the response filed 12/20/01, see page 4-7, it is not routine in the art to screen large numbers of substituted proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. Therefore, one of ordinary skill would require further guidance, such as information regarding the extent of other substitutions

and the location and the specific amino acid changes which would result in the preservation of the stated activity. Therefore, it would require undue experimentation by one of skill in the art to practice the full scope of the invention as claimed.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 61-63, and 93 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,444,792. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims in the patent would anticipate the claims in the instant application and in addition it is obvious that the substitutions recited in the claim in the patent would obviously result in a reduction of a biological effector function of complement activation and Fc receptor interaction and the hinge region would include at least one cysteine available for disulfide bond formation.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 56-59, 65-67, 69, 92, and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Linsley et al (U.S. Patent 5,434,131, filed 5/26/93, IDS 1 ½) and further in view of Gillies et al (Hum. Antibod. Hybridomas 1:47-54, 1990, IDS 1 ½) and Freeman et al (U.S. Patent 6,130,316, filed 7/26/94, IDS 1 ½) and Canfield et al (J. Exp. Med. 173:1483-1491, 1991, IDS 1 ½) and Lund et al (J. Of Immunol. 147:2657-2662, 1992, IDS 1 ½) and Duncan et al (Nature 332:738-740, 1988, IDS 1 ½).

The claims are summarized as a CTLA4-immunoglobulin fusion protein with residues 1-125 of CTLA4 and a immunoglobulin hinge, CH2, and CH3 with modifications at 234 and modifications of leu to glu at 235 and gly to ala at 237.

Linsley et al teach the cloning and expression of human CTLA4, including the extracellular domain which is defined as amino acids 1-125 (see column 4, lines 20-25). Linsley et al further teach the formation and expression of nucleic acids encoding an immunoglobulin fusion protein comprising the extracellular domain of CTLA4 and the constant regions of human IgC 1, including the hinge region, CH1, CH2, and CH3 domains (see entire document, especially colunm 4). Linsley et al does not teach substitutions in the Fc region at specific positions 234, 235, 237. These deficiencies are made up for in the teachings of Gillies et al, Freeman et al, Canfeild et al Lund et al and Duncan et al.

Gillies et al teach modifications to chimeric antibodies, such as deletion of the CH2 domain or substitution of serine for cysteine residues in the hinge region to reduce constant region effector functions such as Fc receptor binding and complement

fixation/activation which in turn reduces other effector functions such as ADCC and complement mediated lysis which Gillies et al teach to be desirable for in vivo applications(see entire document, especially abstract and page 48 and page 52).

Freeman et al teach molecules of CTLA4Ig fusion proteins (see column 6, lines 1-10) and B7-2 immunoglobulin fusion proteins and modifications to the CH2 domain (see column 56-57) at residues 234, 235 and 237 and at cysteines in the hinge to eliminate Fc binding. The Leu at position 234 was replaced by Ala, the Leu 235 was changed to Glu and Gly at position 237 was changed to Ala.

Canfield et al teach that there are two regions within IgG 1, -2, -3, -4 constant regions which are critical for Fc mediated effector functions and that IgG4 has a low binding affinity for Fc. The critical regions are taught to be the hinge (residues 234-239) and the hinge-proximal bend region. Canfield et al teach the Leu at position 234 and Leu at position 235 are critical as well as Pro at position 331. Canfield et al also teach substitutions of several of these positions, including Glu 235 and Ser at 331, to reduce Fc binding and discuss the role of these regions in the engineering of antibodies with desired binding properties (see entire document, especially abstract, page 1484, 1487, 1488, 1490).

Lund et al teach substitutions of Ala for Leu at 234, Ala for Leu at 235, and ala for Gly at 237 to reduce Fc binding functions.

Duncan et al teach substitutions of Ala for Glu at position 318, Ala for Lys at 320, Ala for Lys at 322 to reduce Fc binding function (see page 738).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have modified the immunoglobulin fusion protein of Linsley et al to reduce constant region functions such as Fc binding and complement activation by substituting the specific amino acids at positions 234, 235, 237, 331, 318, 320, or 322 or with Cgamma 4 as taught by Freeman et al or Canfield et al or Lund et al or Gillies et al or Duncan et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have modified the immunoglobulin fusion protein of Linsley et al to reduce constant region functions such as Fc binding and complement activation by substituting the specific amino acids at positions 234, 235, 237, 331, 318, 320, or 322 or with Cgamma 4 as taught by Freeman et al or Canfield et al or Lund et al or Gillies et al or Duncan et al because Freeman et al teach the advantages of modification of the Fc region to enhance the in vivo use. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have modified the immunoglobulin fusion protein of Linsley et al to reduce constant region functions such as Fc binding and complement activation by substituting the specific amino acids at positions 234, 235, 237, 331, 318, 320, or 322 or with Cgamma 4 as taught by Freeman et al or Canfield et al or Lund et al or Gillies et al or Duncan et al because Canfield et al teach specific regions such as those in the hinge region or hinge-link region are necessary for Fc function and Gillies et al teach the desirability of reducing such functions for in vivo applicability. Moreover, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of

success to have modified the immunoglobulin fusion protein of Linsley et al to reduce constant region functions such as Fc binding and complement activation by substituting the specific amino acids at positions 234, 235, 237, 331, 318, 320, or 322 or with Cgamma 4 as taught by Freeman et al or Canfield et al or Lund et al or Gillies et al or Duncan et al because the prior art teaches the known advantages of reducing complement fixation and Fc binding in immunoglobulins and immunoglobulin fusion proteins to enhance in vivo use.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

NOTE: A rejection under of claims 56-59, 65-67 and 92 and 94 would have been made under 35 U.S.C. 103(a) as being unpatentable over Linsley et al (U.S. Patent 5,434,131, issued 7/18/95) and further in view of Lund et al (J. of Immunol. 147:2657-2662, 1991) and Canfield et al (J. Exp. Med. 173:1483-1491, 1991) and Strom et al (U.S. Patent 5,958,403, filed 7/11/94), however, in view of the declaration filed in this application, attachment to #4, the reference of Strom et al is no longer prior art.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

LARRY R. HELMS, PH.D
PRIMARY EXAMINER